Modes of selection: directional, balancing and disruptive

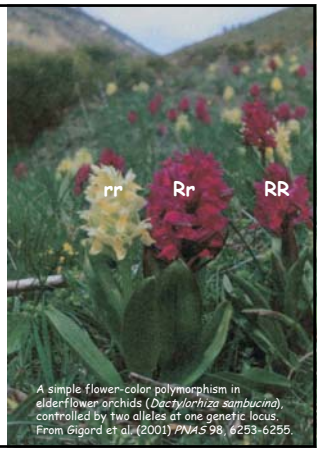
Selection may favor a certain allele unconditionally, regardless of its frequency.

Such *directional* or "positive" selection, if continued, will sooner or later "fix" the favored allele (*i.e.*, increase its frequency to 1.0).

But there are other possibilities!

1. *Balancing* selection keeps two or more alleles at intermediate frequencies and *prevents* fixation.
2. *Disruptive* selection can fix *either* allele, if its frequency is already high enough.

Biol 3410, 4 February 2009



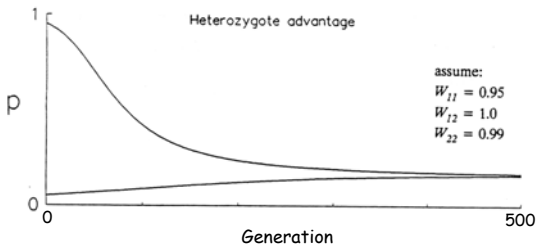
A simple flower-color polymorphism in elderflower orchids (*Dactylorhiza sambucina*), controlled by two alleles at one genetic locus. From Gigord et al. (2001) *PNAS* 98, 6253-6255.

Two kinds of balancing selection: *different* processes, *same* result

Heterozygote advantage: fitness of A_1A_2 > A_1A_1, A_2A_2.

Negative frequency dependence: fitnesses go *down* as frequencies go *up*.

Both are expected to produce stable interior allele-frequency equilibria.



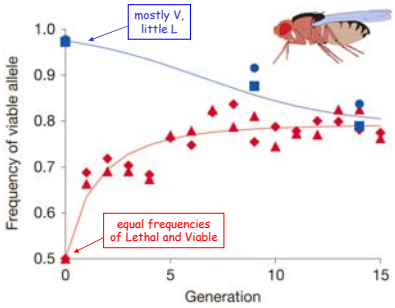
The Mukai and Burdick experiment: another recessive lethal allele

Like Dawson's experiment with flour beetles.

But here the lethal allele (L) is *not* driven extinct by the viable allele (V).

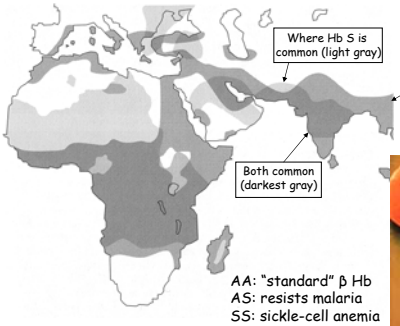
In fact, L *increases* from a low initial frequency!

This implies that VL heterozygotes must be *fitter* than VV homozygotes.



Homework problem: Freeman and Herron estimate the relative fitnesses of the three genotypes as 0.74 : 1 : 0. Derive this result using just a simple extension of our general algebraic model of selection (as explained in lecture and on the handout).

The best-understood case: hemoglobin S and falciparum malaria



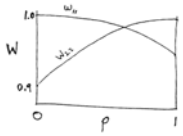
AA: "standard" β Hb
AS: resists malaria
SS: sickle-cell anemia

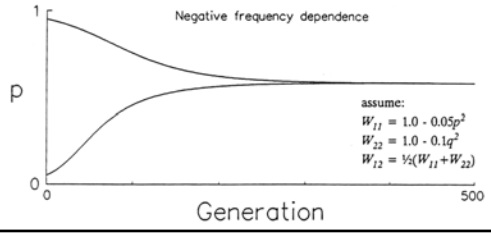
Note how the fitnesses depend on the *environment*: AS is fitter than AA *if* (1) malaria is endemic *and* (2) there is no other defense.

Negative frequency dependence: where I'm my own worst enemy

Here the fitnesses of the *genotypes* (not just the marginal fitnesses of the *alleles*) depend on their own frequencies.

In this made-up example, the fitness of the heterozygote is always half way between those of the homozygotes, so there's never any heterozygote advantage.





Frustrated bumblebees go to differently colored elderflower orchids

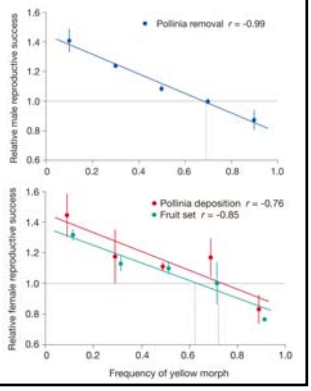
Flowers give *no reward* to bees.

Naïve bees alternate between colors.

The rarer color therefore tends to get more visits per flower.

Fitnesses equalize at P(yellow) = 0.6-0.7 in experimental populations (right).

Natural populations have P(yellow) = 0.69.



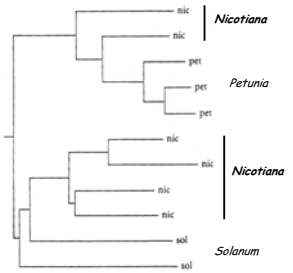
Negative frequency dependence is probably very common

It will arise from competition for resources of almost any kind.

Also escape from diseases, predators and other enemies.

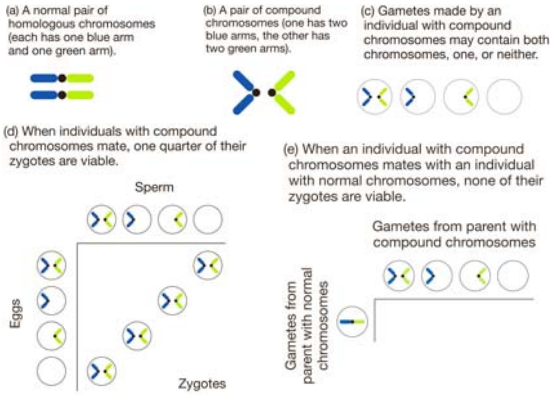
Some classic examples:

- Self-incompatibility alleles in plants (right)
- Sex ratios and mating strategies
- Major histocompatibility (MHC) alleles in all vertebrates



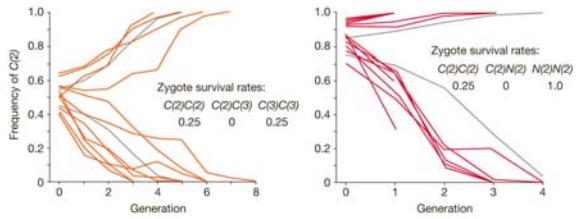
"Trans-specific polymorphism" of self-incompatibility alleles in members of the family Solanaceae. Some S-alleles in tobacco (*Nicotiana*) are more closely related to S-alleles in *Petunia* than to some other S-alleles in their own species!

Disruptive selection (heterozygote disadvantage): an experiment



Theory predicts *unstable* interior equilibria, and they are seen!

(f) Left: Evolution in 11 populations of *Drosophila melanogaster* containing compound second chromosomes [*C*(2)] and compound third chromosomes [*C*(3)]. The initial frequency of *C*(2) ranged from 0.4 to 0.65. Right: Evolution in 13 populations of *Drosophila melanogaster* containing a mixture of compound second chromosomes [*C*(2)] and normal second chromosomes [*N*(2)]. The initial frequency of *C*(2) ranged from 0.71 to 0.96.



Summary

Directional selection *replaces* one allele with another (fitter) allele. At equilibrium the population is monomorphic (fixed) for the fittest allele.

Balancing selection prevents the loss of two or more alleles at a locus, by increasing the marginal fitness of each allele as it becomes rarer. There are two principal mechanisms:
-- heterozygote *advantage* (with fixed genotypic fitnesses)
-- *negative* frequency dependence (with varying genotypic fitnesses)

Disruptive selection favors fixation, like directional selection, but either allele can be the one whose fixation is favored. Again there are two principal mechanisms:
-- heterozygote *disadvantage* ("it's better to be pure")
-- *positive* frequency dependence ("the rich get richer")

All of these processes can be demonstrated in nature.

However, it remains unclear how much genetic variation is maintained by balancing selection (as opposed to other processes that we will discuss later), and of this part, how much is due to heterozygote advantage versus negative frequency dependence.

Given a set of genotypic fitnesses, we can predict evolution.

But where do those fitnesses come from? What *are* they?

The marginal fitnesses of alleles can be viewed as *relative rates of allelic population growth* under a given set of environmental conditions.

Fitnesses of all kinds arise from *interactions* among *genotypes, phenotypes* and *environments* – they are *not* fixed properties of genotypes or phenotypes alone.

Relative and absolute fitnesses

If population size is regulated in a density-dependent manner, then *relative* rates of reproductive success are all that matter.

We are free to set the fitness of one genotype or phenotype (or the *average*) equal to 1, and to scale the others relative to this standard. Then a genotype 10% *worse* than the standard has a fitness of 0.90, and a genotype 10% *better* than the standard has a fitness of 1.10.

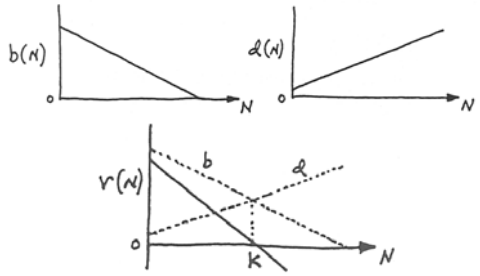
Abstract relative fitnesses of this kind are convenient for models of the evolutionary process, but we need to remember that in fact they arise from *births* and *deaths* in real *ecologies*.

The overall growth rate r is the difference between the birth rate b and the death rate d, and these are functions of the population size N.

$$r(N) = b(N) - d(N)$$

How are b and d expected to depend on N?

Usually births will decline and deaths will increase as *N* increases.



The point where $b = d$ (and $r = 0$) defines the carrying capacity (K).

If these functions are linear (as drawn here), then we get the density-dependent "logistic" growth law: $dN/dt = r(N)N = r(1-N/K)N = rN(1-N/K)$.

What if two genotypes have *different* birth and death functions?

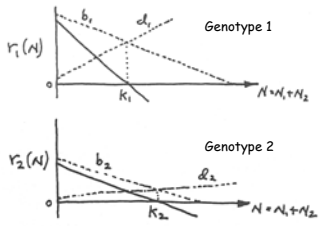
Which genotype has the *higher fitness?*

Clearly, it all depends.

Genotype 1 always has a higher birth rate than genotype 2, and it grows much faster than G2 at low population densities.

But its birth and death rates respond more strongly to $N (=N_1 + N_2)$, so it reaches zero growth at a lower total population size.

Thus G2 can push G1 into *negative* growth, while continuing to grow itself, and thereby take over the world!

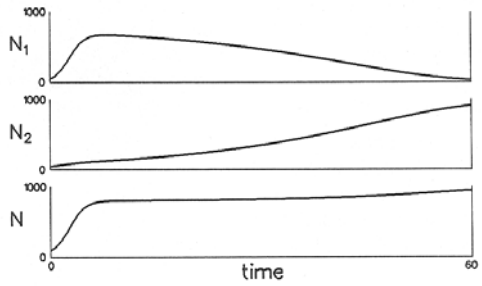


At least this is what it will do in a constant environment. But what if the population occasionally suffers extrinsic mortality that temporarily reduces N to values well below K_1?

Numerical example I (constant environment)

Genotype 1 $r_0(1) = 1.0$ $K(1) = 800$
Genotype 2 $r_0(2) = 0.25$ $K(2) = 1000$

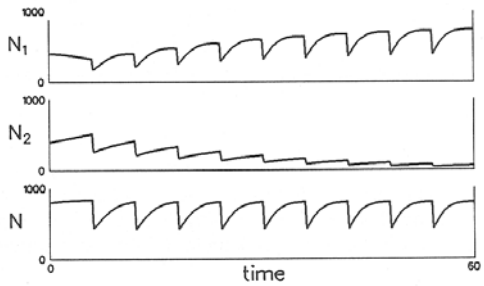
Begin with 50 individuals of each genotype.



Numerical example II (fluctuating environment)

Genotype 1 $r_0(1) = 1.0$ $K(1) = 800$
Genotype 2 $r_0(2) = 0.25$ $K(2) = 1000$

Begin with 400 of each genotype, but kill 50% every 6 time units.



Fitnesses result from *interactions* of genotypes and environments

Factors affecting birth rates
Factors affecting death rates
Composition of the population
Environmental variation (extrinsic to the population)
Past and present
But not the future!

And tradeoffs everywhere!

How and when do typical genes contribute to fitness?

A major puzzle: Most genes appear to be *unnecessary!*

Half or more can be "knocked out" (fully disabled) in yeast, worms, flies and even mice, without any obvious phenotypic effects (in the lab, anyway).

But these genes are maintained in evolution, so they must be useful. *How?*

Two hypotheses:

(1) Most are "special-purpose" genes needed only under certain circumstances (stresses that occur in nature but not in the lab).

(2) Most are "fine-tuning" genes that increase the efficiency or accuracy of some physiological or developmental process in most environments.

Experimental test devised by Joe Dickinson:

Compete "no-phenotype knockouts" against genotypes that are identical except for the knockout, and let natural selection measure their relative fitnesses.

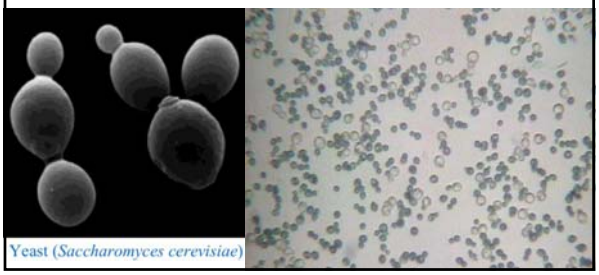
Dickinson talked Janet Shaw (a yeast cell biologist) and John Thatcher (an undergraduate) into helping him try to do this with yeast.

How to ask cells if they miss a (random) gene

Mark either the random, "no-phenotype" knockout, or the wild-type parent, with *lac Z* so that you can score their relative numbers on indicator plates.

Start populations with equal numbers of wild-type and knockout cells; grow them for many generations in complete (rich) liquid media.

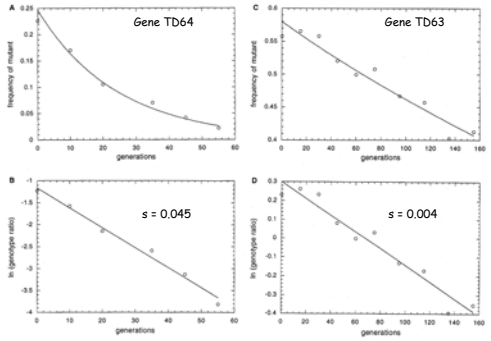
Sample the populations every 10-20 generations and score the relative numbers of marked and unmarked cells.



Yeast (*Saccharomyces cerevisiae*)

Plot the frequency of the knockout as a function of generations (A, C)

Also plot the log of the ratio of the allele frequencies [ln(q/p)] versus generation (B, D). The slope of this (straight) line is an estimate of the selection coefficient (*s*).



Summary of results for 27 "no-phenotype" knockouts

Nineteen mutations (70%) showed statistically significant fitness defects ranging from 0.3% (*s* = 0.003) to 23% (*s* = 0.23).

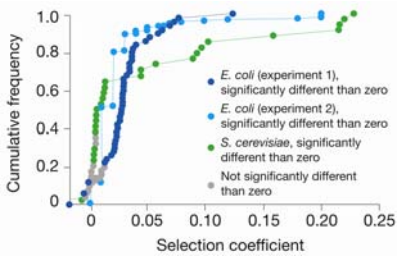
Among these, the typical (median) selection coefficient was 1-2%.

Six mutations (22%) were not statistically distinguishable from neutral. (Five of the six appeared to be weakly deleterious, and one appeared to be beneficial.)

A more sensitive experimental design (with larger populations and allele-frequency assays) would probably show most of these to be significant, raising the fraction of deleterious no-phenotype knockouts to 85-90%.

Two of the 27 knockouts (7%) were significantly *advantageous*, with "negative" coefficients of *s* = -0.005 and *s* = -0.007.

Conclusion: Most genes make *modest* contributions to fitness



This finding (in bacteria, too) supports the "fine-tuning" hypothesis.

Such small effects *could not be detected except by natural selection.*

Read the paper: Thatcher, Shaw & Dickinson, *PNAS* **95**, 253-257 (1998).

And hey! What about those crazy knockouts that *increased* fitness?